

Fi



Europäisches Patentamt
European Patent Office
Office européen des brevets



Publication number: **0 268 460 B1**

(12)

EUROPEAN PATENT SPECIFICATION

- (45) Date of publication of patent specification: **06.11.91** (51) Int. Cl.⁵: **A61K 47/00, //C07D317/12, C07D317/16, C07D317/20, C07D319/06**
- (21) Application number: **87310141.4**
- (22) Date of filing: **17.11.87**

(54) **New percutaneous absorption enhancers, compositions containing same and method of use.**

- (30) Priority: **17.11.86 US 931653**
- (43) Date of publication of application: **25.05.88 Bulletin 88/21**
- (45) Publication of the grant of the patent: **06.11.91 Bulletin 91/45**
- (84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE
- (56) References cited:
EP-A- 0 012 543
DE-B- 1 082 370
GB-A- 1 385 914
GB-A- 2 141 025

CHEMICAL ABSTRACTS, vol. 96, no. 4, 25th January 1982, page 301, abstract no. 24742b, Columbus, Ohio, US; J.M. FRANZ et al.: "Percutaneous absorption of griseofulvin and proquazone in the rat and in isolated human skin"

- (73) Proprietor: **Macrochem Corporation**
9 Linnell Circle
Billerica, Massachusetts 01821(US)
- (72) Inventor: **Samour, Carlos M.**
324 Linden Street
Wellesley Massachusetts 02181(US)
Inventor: **Daskalakis, Stefanos**
116 Early Street
Morristown New Jersey 07960(US)
- (74) Representative: **Adams, William Gordon et al**
RAWORTH, MOSS & COOK 36 Sydenham Road
Croydon Surrey CR0 2EF(GB)

EP 0 268 460 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

Description

The present invention relates to a method for enhancing skin penetration of therapeutic agents utilizing certain 1,3-dioxacyclopentanes and 1,3-dioxacyclohexanes and compositions containing such compounds as well as to new penetration enhancing compounds within these chemical classifications.

The desirability of the delivery of physiologically active agents through the skin, i.e. transdermally, as opposed to other methods of parenteral administration or via the digestive system is based on many factors. The large surface area of the skin (over 3,000 square inches for the average adult) and the large circulatory (about one-third of total body blood) and lymphatic networks available near the skin, the generally non-invasive nature of topical applications and their delivery through the skin, the convenience, the safety, the potential greater control of delivered agents, and the minimal side effects are just some of the advantages seen for this technique.

While not every and all agents may be suitable for transdermal delivery because of local irritation, allergic reactions, etc., most are indicated as suitable but, unfortunately, the greatest problem is overcoming the general barrier to drug penetration (or indeed to any materials) of the skin. A drug must pass through the outer layer of skin or epidermis and into the dermis layer before being absorbed into the blood stream. The epidermis comprises two main parts, the stratum corneum and the stratum germinativum. The stratum corneum forms the outermost layer of the epidermis and consists of many stratified layers of compacted, flattened, keratinized cells which have lost their nuclei. This outermost layer serves as a physical barrier to light, heat, microorganisms, and most chemical agents. In addition, it behaves as a primary barrier to percutaneous absorption. Because of the barrier effect of the skin, it has heretofore only been possible to deliver drugs that are "low-dose" drugs, in the range of 10 mg/day or less, or those of low molecular weight. In addition they have to have the proper lipophilic-hydrophilic balance to permit adequate absorption. It was recognized as early as the beginning of this century that lipid-soluble substances, such as nonelectrolytes have a comparatively greater skin permeability than water-soluble substances, such as electrolytes.

The phenomenon of percutaneous absorption or transdermal permeation can be viewed as a composite of a series of steps in sequence, that is, adsorption of a penetrant molecule onto the surface layers of stratum corneum, diffusion through it and through the viable epidermis, and finally through the papillary dermis and into the microcirculation. The great diffusional resistance of stratum corneum has been demonstrated in a comparative absorption of drugs, like hydrocortisone. The mucous membranes in the rectal and vaginal regions permit the absorption of 26-29% of the steroid applied, while less than 2% of the applied dose is absorbed through the skin.

Compounds which are known or reported to enhance the transdermal delivery of drugs include dimethyl sulfoxide (DMSO), polyethylene glycol monolaurate, alkyl lactams, and long-chain amides. Prior art patents of relevance to penetrating enhancers for physiologically active agents include U.S. Patent 3,551,554 which describes dimethyl sulfoxide; U.S. Patent 3,989,816 discloses 1-substituted azacycloheptane-2-one; U.S. Patent 4,132,781 discloses a topical antibiotic plus 2-pyrrolidone or an n-lower alkyl-2-pyrrolidone U.S. Patent 4,017,641 also describes 2-pyrrolidone but with propylene glycol; others of interest are U.S. Patent 3,903,256; 4,343,798, 4,046,886; 3,934,013; 4,070,462; 4,130,643; 4,130,667; 4,289,764; 4,070,462; 3,527,864; 3,535,422; 3,598,123; 3,952,099; 4,379,454; 4,286,592; 4,299,826; 4,314,557; 4,343,798; 4,335,115; 3,598,122; 4,405,616; 3,896,238; and 3,472,931 and U.S. Patent 4,557,934

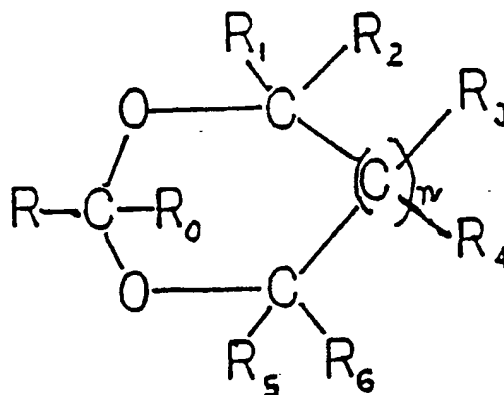
None of the references cited heretofore discloses any 1,3-dioxolane or 1,3-dioxane and especially any of the substituted types previously mentioned and hereinafter described for use as percutaneous absorption enhancers for physiologically active substances.

The present invention relates to a class of compounds which are effective in enhancing the transport of a large number of higher-dose, poorly-absorbed drugs through the skin.

The compounds which are provided by and for use in this invention are substituted 1,3-dioxacyclopentanes and substituted 1,3-dioxacyclohexanes.

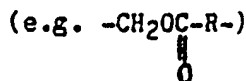
The compounds have the general formula:

I



wherein R, R₀, R₁, R₂, R₃, R₄, R₅, and R₆ are each independently selected from hydrogen and C₁ to C₁₈ aliphatic groups, preferably alkyl, alkenyl, halo, hydroxy, carboxy, carboxamide, and carboalkoxy substituted forms thereof, with at least one of said R's an alkyl or alkenyl group of C₄ to C₁₈ and n=0 or 1; the total number of carbon atoms in all of said R groups being no more than 40 and preferably less than 20 and not more than 1 thereof containing 18 or more carbon atoms.

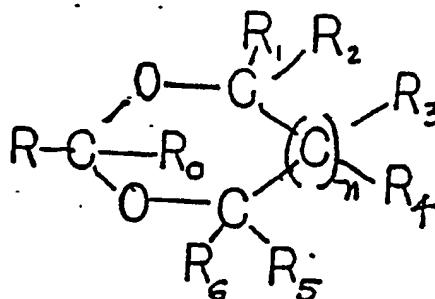
Preferred compounds with the general formula (I) are those where R is C₄ to C₁₈ and preferably C₆ to C₁₂ and more preferably C₇ to C₁₀. Another preferred class are the cyclopentanes (i.e. dioxananes) which R & R₀ are hydrogen and one R₁, R₂, R₅ & R₆ is C₄ to C₁₈, preferably C₆ to C₁₂ and more preferably C₇ to C₁₀. The preferred moieties for the R groups are alkyl, alkenyl, carboalkoxy



or $-\text{CH}_2\text{OR}$.

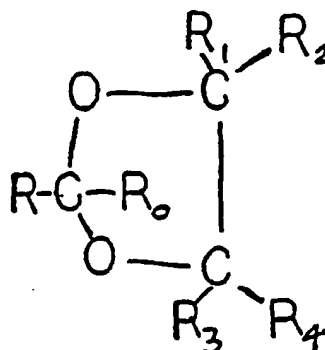
General formula representing most preferred enhancers are the following:

II.



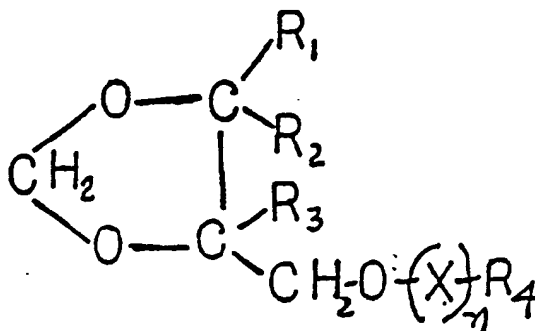
where R is C₄ to C₁₈ and preferably C₆ to C₁₂ to most preferably C₇ to C₁₀ and the other R groups are lower moieties (C₁ and C₄) or any of the other groups such as hydrogen, halo, carboxy, hydroxy, amid and the like, and n=0 or 1; and

III.

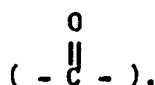


where one of the R groups is C₄ to C₁₈, preferably C₆ to C₁₂ and more preferably C₇ to C₁₀ and the others are as in formula II; and

IV.



where R is C₄ to C₁₈, preferably C₆ to C₁₂ and more preferably C₇ to C₁₀ and R₁, R₂ and R₃ are again as the others in formulae II and III, n=0 or 1 and when n=1, X is carbonyl



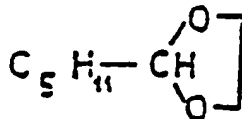
In Formulae II and III, it is preferred that R₆ is hydrogen. In Formula III it is also preferred that R is also hydrogen.

The compounds contemplated herein may be applied in conjunction with any agent it is desired to transdermally administer to humans and animals, as in admixture therewith. It is also often desirable to pretreat the skin immediately before (e.g. for several minutes or longer i.e. 15 minutes, 30 minutes, one hour, etc.) or after, e.g. in immediate sequence or after 15 minutes, or 30 minutes, or one hour, or 10 hours or 24 hours etc. The dioxane or dioxolane with or without therapeutic agents or other additives may be incorporated into any suitable substrate as by coating, or impregnation. It may be admixed with a hydrophilic or hydrophobic material and in this form coated onto a suitable substrate, or formed into a film (e.g. using a film-forming hydrophilic or hydrophobic resin such as polyethylene, nylon, polyester, polyurethane, hydrolyzed (e.g. 85%) polyvinyl acetate, cellulose acetate, regenerated cellulose, etc.) and used as a self-sustained film or laminated or otherwise joined to another substrate e.g. paper, metal, non-woven (resin or spun-bonded) fabrics, woven fabrics (e.g. cotton, rayon, nylon, polyester and the like). The enhancer alone or with medicant (agent to be administered) and/or additives may be dissolved or dispersed in one of the foregoing thermoplastic resins or in any other as well and melt spun or calendered or molded into any desired shape or structure. A very useful substrate for the enhancer per se or in combination with a physiologically active agent is in a pressure-sensitive adhesive mostly generally in association with any carrier base (e.g. plastic, paper, cloth, metal, foil, etc.). It is of course obvious that many of the usual adjuvants commonly or otherwise utilized and/or administered with the selected physiologically active agent can be employed in the various compositions, articles and processes contemplated and described herein.

Such adjuvants include, inter alia, solvents such as water, ethanol, etc., lipid materials, coloring agents, fragrances, anti-oxidants, thickening agents, ultra-oxidants, thickening agents, ultra-violet light stabilizers, preservatives, and others conventional in such compositions.

5 Example I

Preparation of 2-n-pentyl-1,3 dioxolane (1)

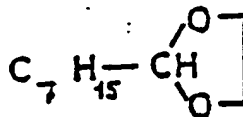


10

15 30 g (0.29 mole) of hexanal, 31 g (0.5 mole) of ethylene glycol, 100 mg of p-toluenesulfonic acid (p-Ts) in 100 ml of benzene are placed in 250 ml round-bottomed flask equipped with a Dean-Stark trap, a condenser and a mechanical stirrer. The mixture is heated to reflux until no more water has separated from the benzene phase. The mixture is then cooled to room temperature, washed with 100 ml of 5% sodium
20 bicarbonate, 100 ml of saturated NaCl solution, and finally water. The solution is dried over sodium sulfate. After removing the solvent, the oil is fractionated. A yield of 19.6 g of colorless oil (46%) is obtained $n_D^{20} = 1.4554$.

Example II

25 Preparation of 2-n-heptyl-1,3 dioxolane (2)

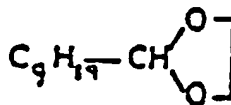


30

Following procedure given for compound I, from 30 g (0.23 mole) of octyl aldehyde, 31 g (0.5 mole) of
35 ethylene glycol, 100 mg of p-Ts. in 70 ml of benzene there is obtained 20.5g (50.9%) of a colorless oil. $n_D^{20} = 1.4336$.

Example III

40 Preparation of 2-n-nonyl-1,3 dioxolane (3)



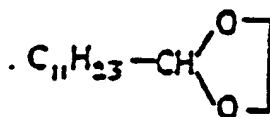
45

Following example I, from 78.77 g of decylaldehyde (0.5 mole), 37.22 g (0.6 mole) of ethyleneglycol, 0.5 g
50 of p-toluenesulfonic acid in 100 ml toluene there is obtained 79 g (77.4%) of a colorless product; b.p. $80^\circ - 81^\circ \text{C}/0.5 \text{ mm}$. $n_D^{20} = 1.4392$.

Example IV

Preparation of 2-n-undecyl-1,3 dioxolane

55



5

Following example I, 45.56 g (0.25 mole) of dodecyl aldehyde, 17.85 g (0.288 mole) of ethyleneglycol, 0.02 g of paratoluenesulfonic acid in 140 ml toluene are reacted to obtain 30 g (55%) of a colorless product; b.p. 112°-116° C/1.5 mm. $n_D^{20} = 1.9999$.

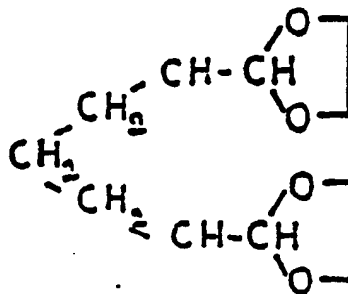
10

Example VPreparation of pentylene-1,5-bis-1,3 dioxolane (5)

15

20

25



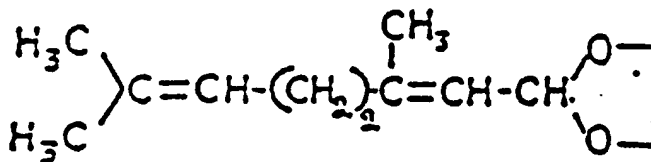
Following procedure given for compound 1, 32 g (0.31 mole) of glutaraldehyde, 52.01 g (0.83 mole) of ethylene glycol, 200 mg. of p-Ts. in 150 ml of benzene are reacted to yield 46.03 g (67%) of a colorless oil having an $n_D^{20} = 1.4559$. b.p. = 0.1 mm/78-82° C.

30

Example VIPreparation of 2-(2',6'-dimethyl-2',6'-heptadienyl)-1,3 dioxolane (6)

35

40



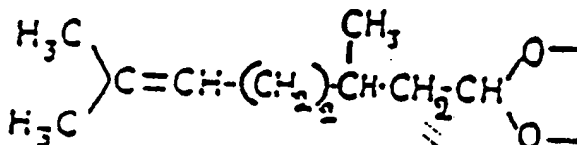
Following example I, from 50 g (0.32 mole) of citral 24.8 g (0.4 mole) ethyleneglycol, 0.02 g of p-toluenesulfonic acid in 75 ml benzene is obtained 18.2 g of a light yellow oil; $n_D^{20} = 1.4940$; b.p. = 0.5 mm/34-36° C.

45

Example VIIPreparation of 2-(2',6'-dimethyl-2'heptaenyl)-1,3 dioxolane (7)

50

55

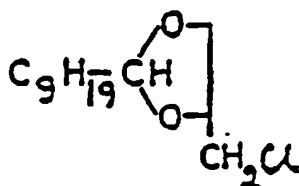


10

30.58 g of 80% citronellal (0.158 mole) is placed in a 500 ml flask equipped with a distilling receiver, condenser equipped with a drying tube and a magnetic stirrer. 14.59 g of ethylene glycol (0.23 mole) and 0.02 g of p-toluenesulfonic acid in 100 ml of dry benzene is then added and the mixture is heated to reflux under stirring until no more water has separated in the distilling receiver (about 6 hours). Upon completion of the reaction the mixture is washed with 2 x 10 ml (5%) sodium bicarbonate solution, water and dried over sodium sulfate. The reaction mixture is filtered and the filtrate is concentrated to a yellow oil. Distillation yields 17.57 g (41%) of a colorless product; b.p. $65^\circ - 70^\circ \text{C}/0.5 \text{ mm}$. $n_D^{20} = 1.4645$.

Example VIII
Preparation of 2-n-nonyl-5-chloromethyl-1,3 dioxolane (8)

25

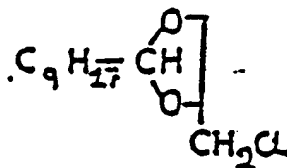


30

Following procedure given for compound I, from 24.95 g (0.16 mole) of decyl-aldehyde, 17.6 g (0.16 mole) of 3-chloro-1,2-propanediol, 0.2 g of p-Ts. in 100 ml of toluene there is obtained 30.49 g of a colorless oil (77%); b.p. = $0.14 \text{ mm}/91-100^\circ \text{C}$. $n_D^{20} = 1.4533$.

Example IX
Preparation of 2-(2',6'-dimethyl-2'-heptaenyl)-1,3 dioxolane (9)

40

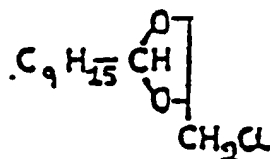


45

Following procedure given for compound I, from 15 g (0.097 mole) of 3-chloro-1,2-propanediol, 10 g (0.06 mole) of citronellal, 150 mg p-Ts. in 75 ml of benzene there is obtained 12.56 g of a crude product (oil).

Example X
Preparation of 2(2',6'-dimethyl-2',6'-heptadienyl)-5-chloromethyl-1,3 dioxolane

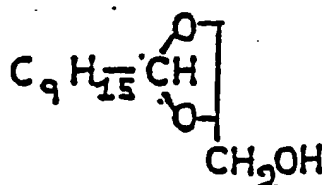
55



Following procedure given for compound I from 12.77 g (0.08 mole) of citral, 10 g (0.09 mole) of 3-chloro-1,2 propadiol, 60 mg of p-Ts in 50 ml of benzene there is obtained 10.7 g of raw oil (54.7%).

Example XI

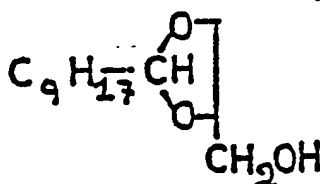
Preparation of 2-(2',6'-dimethyl-2',6'-heptadienyl)-5-hydroxymethyl 1,3-dioxolane



Following example I, 51.4 g (0.33 mole) of citral 46 g (0.5 mole) of glycerol and 0.04 g of p-toluenesulfonic acid in 150 ml benzene are reacted to give 31.45 g of a colorless oil (41.11%) $n_D^{20} = 1.4963$.

Example XII

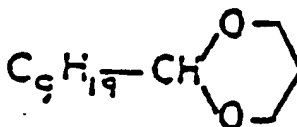
Preparation of 2-(2',6'-dimethyl-2'-heptaenyl)-5-hydroxymethyl-1,3 dioxolane



Following procedure given for product I, from 27.62 g (0.3 mole) of glycerol, 17.2 ml of citronellal (0.1 mole), 400 mg of p-Ts in 150 ml toluene there is obtained 9.69 g of an oil.

Example XIII

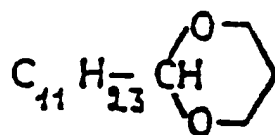
Preparation of 2-n-nonyl-1,3 dioxane



Following example I from 78.77 g of decylaldehyde (0.5 mole), 45.65 g (0.6 mole) of 1,3 propandiol 0.5 g of p-toluenesulfonic acid in 100 ml toluene are reacted to obtain 67.69 (62.65% of a colorless product with a b.p. 70-74 °C/0.1 mm. Hg and an $n_D^{20} = 1.4448$.

Example XIV

Preparation of 2-n-undecyl-1,3 dioxane



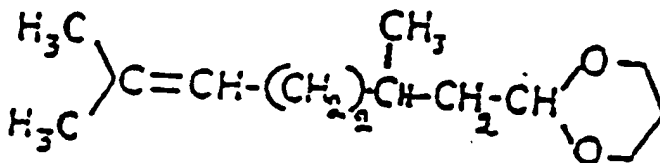
5

Following procedure given for product I, from 11.19 g (0.064 mole) of dodecylaldehyde, 7.5 g (0.098 mole) of 1,3 propandiol, 50 mg. of p-Ts in 50 ml of benzene there is obtained 7.46 g (48%) of a colorless oil with an $n_D^{20} = 1.4477$ and a b.p. = 0.065 mm/89° C.

Example XVPreparation of 2-(2',6'-dimethyl-2'-heptaenyl)-1,3 dioxane

15

20



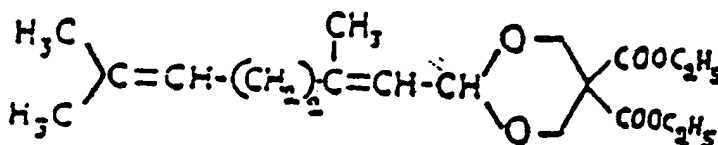
10 g of 80% citronellal (64 mole) is placed in a 250 ml flask equipped with a distilling receiver, condenser equipped with a drying tube and a magnetic stirrer. 7.5 g of 1,3 propandiol (0.098 mole) and 0.05 g of p-toluenesulfonic acid in 50 ml of dry benzene is then added and the mixture is heated to reflux under stirring until no more water separates in the distilling receiver (about 6 hours). Upon completion of the reaction the mixture is washed with 2 x 10 ml (5%) sodium bicarbonate solution, water and dried over sodium sulfate. The reaction mixture is filtered and the filtrate is concentrated to a yellow oil. Distillation yields 17.57 g (72.6%) of colorless product; b.p. 65-70° C/0.5 mm. $n_D^{20} = 1.4609$.

30

Example XVIPreparation of 2-(2',6'-dimethyl-2',6-heptadienyl)-5-(bis ethylcarboxylate)-1,3 dioxane (18)

35

40



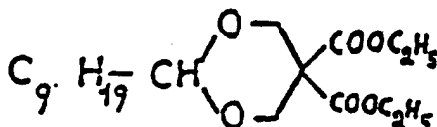
Following procedure given for compound XV, from 9.13 g (0.06 mole) of citral, 20 g (0.09 mole) of ethyl (bis-hydroxymethyl)malonate and 0.3 g of p-toluenesulfonic acid in 60 ml of benzene there is obtained a light yellow oil with a b.p. = 0.5 mm. Hg/140° C and an $n_D^{20} = 1.4761$.

45

Example XVIIPreparation of 2-n-nonyl-5-(bis ethylcarboxylate)-1,3 dioxane

50

55



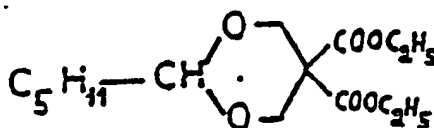
5.2 of decyl aldehyde (0.33 mole) is placed in a 100 ml flask equipped with a distilling receiver, condenser

equipped with a drying tube and magnetic stirrer. 8.53 g (0.0387 mole) of ethyl(bis-hydroxymethyl)malonate and 0.2 g of p-toluenesulfonic acid in 50 ml of dry benzene is then added and the mixture is heated to reflux under stirring until no more water separates in the distilling receiver (about 6 hours). Upon completion of the reaction the mixture is washed with 2 x 10 ml (5%) sodium bicarbonate solution, water and dried over sodium sulfate. The reaction mixture is filtered and the filtrate is concentrated to a yellow oil. Distillation yields 8.96 g (74.1%) of a colorless product with the following properties; b.p. = 0.22 mm Hg/150° C; $n_D^{20} = 1.4490$

Example XVIII

10 Preparation of 2-n-pentyl-5-(bis-ethylcarboxylate)-1,3 dioxane

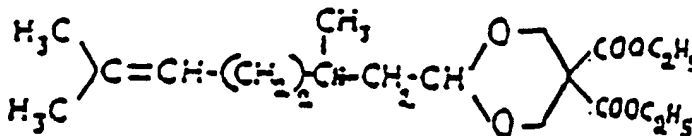
15



20 6 g of hexyl aldehyde (0.05 mole) is placed in a 100 ml flask equipped with a distilling receiver, condenser equipped with a drying tube and magnetic stirrer. 20 g (0.09 mole) of ethyl(bis-hydroxymethyl) malonate and 0.2 g of p-toluenesulfonic acid in 60 ml of dry toluene is then added and the mixture is heated to reflux under stirring until no more water separates in the distilling receiver (about 6 hours) Upon completion of the reaction, the mixture is washed with 2 x 10 ml (5%) sodium bicarbonate solution, water and dried over sodium sulfate. The reaction mixture is filtered and the filtrate is concentrated to a yellow oil. Distillation yields 11.19 g (62%) colorless product; b.p. = 0.2/100-118° C; $n_D^{20} = 1.4453$.

Example XIX

30



35

Following procedure given for compound XV from 9.25 g (0.06 mole) of citronellal, 20 g (0.09 mole) of ethyl(bis-hydroxymethyl)malonate and 0.3 g of p-toluenesulfonic acid in 60 ml of benzene there is obtained 40 3.5 g of a colorless oil with the following properties; b.p. = 0.3 mm/135° C; $n_D^{20} = 1.4751$.

The compounds of Examples III, IV, V, VI, VIII, XIII, XIV, and XV were tested in vitro using hairless rat skin and a diffusion cell procedure which closely simulates the in vivo situation because the skin is exposed to ambient conditions. The flow-through diffusion cell uses a perfusion of the dermal side of the skin. The sampling is facilitated by an automatic collection of the liquid continuously around the clock. The cells are designed with a water jacket to provide a temperature control and equilibrium of the skin and the dermal liquid.

The general method is as follows. The skin is mounted in the cell and allowed to equilibrate with the environmental conditions for 5 hours ($20 \pm 1^\circ \text{C}$). The water-jacket temperature is 37°C and the liquid in the dermal compartment is diluted bovine albumin in saline water (1.5% w/v). Antibiotics are added in the bathing solution to avoid bacterial development. 500 mg of the test drug in 0.1 ml of ethanol/water (95/5 w/v) mixture are applied on the epidermal surface. After application, the solvent is allowed to evaporate between 1 and 2 hours, and the solid drug deposit remains on the skin. The drug to be tested in a radioactive compound and its absorption flux is monitored after the application of the radioactive mixture by sampling the radioactivity in samples of the dermal solution at hourly intervals during 48 hours. After 24 hours following the drug application, 0.1 ml of the enhancer is applied on the treated area.

Following the procedure outlined above the compound of Example III when tested with progesterone, caffeine and indomethacin shows markedly increased skin diffusion when the Example III enhancers is

applied to the skin following the drug application. Thus, for example, during the first 24 hours period (drug alone-no enhancer application) the % indomethacin diffused is 1.47%/cm² while after 48 hours (24 hours after application of enhancer) the % is 12.85%/cm²; with progesterone it is found that compound of Example III is 10 times more effective than alcohol of N-dodecyl caprolactam (a reported enhancer).

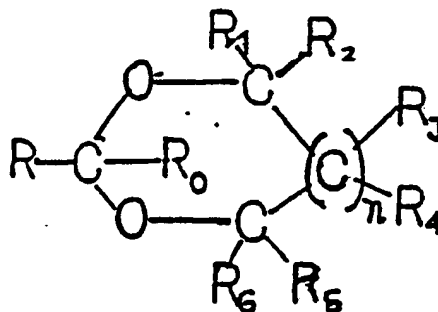
In a similar vein, compounds of Examples IV, V, VI, VIII, XIII, XIV, and XV are found to be outstandingly effective.

In other tests the total % percutaneous absorption after 48 hours (drug first for 24 hours then application of enhancer) shows the following results:

<u>Composition</u>	<u>Drug</u>		<u>Indomethacin</u>
	<u>Progesterone</u>	<u>Caffeine</u>	
1. Drug alone	4.9	7.7	1.7
2. Cpd. Ex VI	11.98	52.4	5.3
3. Cpd. Ex IV	9.55	54.4	7.0
4. Cpd. Ex III	14.3	47.6	14.3
5. Cpd. Ex VIII	11.0	11.4	1.8

Claims

1. A therapeutic composition suitable for transdermal administration to humans and animals comprising a physiologically active agent and as an effective skin penetration enhancer a pharmaceutically acceptable 1,3-dioxacyclopentane or 1,3-dioxacyclohexane each of which contains at least one aliphatic group having 4 to 18 carbon atoms.
2. A therapeutic composition suitable for transdermal administration to humans and animals comprising a physiologically active agent and an effective skin penetration enhancer as claimed in Claim 1 having the formula:



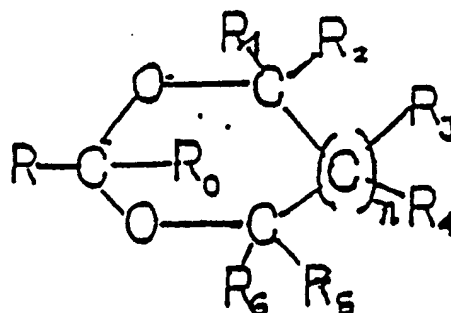
wherein R, R₀, R₁, R₂, R₃, R₄, R₅, and R₆ are each independently selected from hydrogen and C₁ to C₁₈ aliphatic groups, preferably alkyl, alkenyl, halo, hydroxy, carboxy, carboxyamide, and carboalkoxy substituted forms thereof, with at least one of said R's an alkyl or alkenyl group of C₄ to C₁₈, and n=0 or 1; the total number of carbon atoms in all of said R groups being no more than 40, and preferably less than 20 and not more than 1 thereof containing 18 or more carbon atoms.

3. A therapeutic composition as claimed in Claim 2 where n=0.

4. A therapeutic composition as claimed in Claim 2 where $n = 1$.
5. A therapeutic composition as claimed in Claim 3 wherein $R = C_5$ to C_{10} aliphatic moiety.
- 5 6. A therapeutic composition as claimed in Claim 5 where R is n -pentyl.
7. A therapeutic composition as claimed in Claim 5 where R is nonyl.
8. A therapeutic composition as claimed in Claim 5 where R is undecyl.
- 10 9. A therapeutic composition as claimed in Claim 5 where R is 2,6-dimethyl-2,6- heptadienyl.
10. A therapeutic composition as claimed in Claim 7 where R_1 , R_2 , and R_5 are hydrogen and R_6 is chloromethyl.
- 15 11. A therapeutic composition as claimed in Claim 7 where R_1 , R_2 and R_5 are hydrogen and R_6 is hydroxymethyl.
12. A therapeutic article suitable for enhancing the transdermal administration to humans and animals of a physiologically active agent comprising a substrate and a pharmaceutically acceptable 1,3- diox-
20 acyclopentane or 1,3- dioxacyclohexane each of which contains an aliphatic group having 4 to 18 carbon atoms.
13. A therapeutic article as claimed in Claim 12 wherein the substrate is a hydrophilic or hydrophobic film.
- 25 14. A therapeutic article as claimed in Claim 13 wherein the film is a hydrogel.
15. A therapeutic article as claimed in Claim 13 wherein the film is a pressure-sensitive adhesive.

30 Revendications

1. Composition thérapeutique appropriée pour l'administration transcutanée chez l'homme et les animaux, comprenant un agent physiologiquement actif et, en tant que renforteur efficace de la pénétration cutanée, un 1,3-dioxacyclopentane ou 1,3-dioxacyclohexane pharmaceutiquement acceptable, dont
35 chacun contient au moins un groupe aliphatique comportant 4 à 18 atomes de carbone.
2. Composition thérapeutique appropriée pour l'administration transcutanée chez l'homme et les animaux, comprenant un agent physiologiquement actif et un renforteur efficace de la pénétration cutanée, selon la revendication 1, répondant à la formule :



55 dans laquelle R , R_0 , R_1 , R_2 , R_3 , R_4 , R_5 , et R_6 , sont choisis chacun indépendamment parmi l'hydrogène et les groupes aliphatiques en C_1 à C_{18} , de préférence sous leur forme substituée par un groupe alkyle, alcényle, halogéno, hydroxy, carboxy, carboxyamide et carboalcoxy, étant entendu qu'au moins

l'un des R est un groupe alkyle ou alcényle en C₄ à C₈ et que n = 0 ou 1 ; le nombre total des atomes de carbone dans tous lesdits groupes R n'étant pas supérieur à 40, et de préférence inférieur à 20, et parmi eux, pas plus d'un comprenant 18 ou plus d'atomes de carbone.

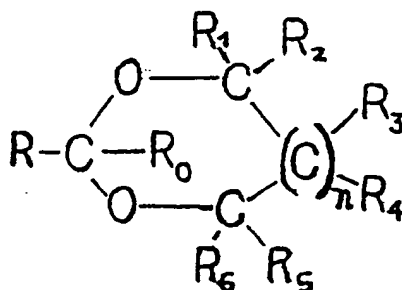
- 5 3. Composition thérapeutique selon la revendication 2, dans laquelle n = 0.
4. Composition thérapeutique selon la revendication 2, dans laquelle n = 1.
- 10 5. Composition thérapeutique selon la revendication 3, dans laquelle R est un groupe aliphatique en C₅ à C₁₀.
6. Composition thérapeutique selon la revendication 5, dans laquelle R est un groupe n-pentyle.
7. Composition thérapeutique selon la revendication 5, dans laquelle R est un groupe nonyle.
- 15 8. Composition thérapeutique selon la revendication 5, dans laquelle R est un groupe undécyle.
9. Composition thérapeutique selon la revendication 5, dans laquelle R est un groupe 2,6-diméthyl-2,6-heptadiényle.
- 20 10. Composition thérapeutique selon la revendication 7, dans laquelle R₁, R₂ et R₅ représentent un atome d'hydrogène et R₆ représente un groupe chlorométhyle.
- 25 11. Composition thérapeutique selon la revendication 7, dans laquelle R₁, R₂ et R₅ représentent un atome d'hydrogène et R₆ représente un groupe hydroxyméthyle.
- 30 12. Article thérapeutique approprié pour renforcer l'administration transcutanée chez l'homme et les animaux d'un agent physiologiquement actif, comprenant un substrat et un 1,3-dioxacyclopentane ou 1,3-dioxacyclohexane pharmaceutiquement acceptable, dont chacun contient un groupe aliphatique comportant 4 à 18 atomes de carbone.
13. Article thérapeutique selon la revendication 12, dans lequel le substrat est un film hydrophile ou hydrophobe.
- 35 14. Article thérapeutique selon la revendication 13, dans lequel le film est un hydrogène.
15. Article thérapeutique selon la revendication 13, dans lequel le film est un adhésif sensible à la pression.

Patentansprüche

- 40 1. Therapeutische Zusammensetzung, die zur transdermalen Verabreichung an Menschen und Tieren geeignet ist und ein physiologisch aktives Mittel und als wirksamen Hautdurchdringungsverbesserer ein pharmazeutisch annehmbares 1, 3-Dioxacyclopentan oder 1,3-Dioxacyclohexan, die jeweils wenigstens eine aliphatische Gruppe mit 4 bis 18 Kohlenstoffatomen enthalten, umfaßt.
- 45 2. Therapeutische Zusammensetzung, die zur transdermalen Verabreichung an Menschen und Tieren geeignet ist, umfassend ein physiologisch aktives Mittel und einen wirksamen Hautdurchdringungsverbesserer nach Anspruch 1 mit der Formel

50

55



5 worin R, R₀, R₁, R₂, R₃, R₄, R₅ und R₆ jeweils unabhängig aus Wasserstoff und C₁-C₁₈-aliphatischen Gruppen, vorzugsweise Alkyl, Alkenyl, Halogen, Hydroxy, Carboxy, Carboxamid und carboalkoxysubstituierte Formen hievon ausgewählt sind, wobei wenigstens eines der R eine C₄-C₈-Alkyl- oder Alkenylgruppe darstellt und n = 0 oder 1 ist; wobei die Gesamtzahl der Kohlenstoffatome in allen Gruppen R nicht größer als 40, vorzugsweise kleiner als 20, ist und nicht mehr als eine hievon 18 oder mehr Kohlenstoffatome enthält.

- 20 3. Therapeutische Zusammensetzung nach Anspruch 2, wobei n = 0 ist.
4. Therapeutische Zusammensetzung nach Anspruch 2, wobei n = 1 ist.
5. Therapeutische Zusammensetzung nach Anspruch 3, wobei R ein C₅-C₁₀-aliphatischer Rest ist.
- 25 6. Therapeutische Zusammensetzung nach Anspruch 5, wobei R n-Pentyl darstellt.
7. Therapeutische Zusammensetzung nach Anspruch 5, wobei R Nonyl darstellt.
- 30 8. Therapeutische Zusammensetzung nach Anspruch 5, wobei R Undecyl darstellt.
9. Therapeutische Zusammensetzung nach Anspruch 5, wobei R 2,6-Dimethyl-2,6-heptadienyl darstellt.
10. Therapeutische Zusammensetzung nach Anspruch 7, wobei R₁, R₂ und R₅ Wasserstoff bedeuten und R₆ Chlormethyl darstellt.
- 35 11. Therapeutische Zusammensetzung nach Anspruch 7, wobei R₁, R₂ und R₅ Wasserstoff bedeuten und R₆ Hydroxymethyl darstellt.
- 40 12. Therapeutischer Artikel, der zur Verbesserung der transdermalen Verabreichung eines physiologisch aktiven Mittels an Menschen und Tieren geeignet ist und ein Substrat und ein pharmazeutisch annehmbares 1,3-Dioxacyclopentan oder 1,3-Dioxacyclohexan, die jeweils eine aliphatische Gruppe mit 4 bis 18 Kohlenstoffatomen enthalten, umfaßt.
- 45 13. Therapeutischer Artikel nach Anspruch 12, wobei das Substrat ein hydrophiler oder hydrophober Film ist.
14. Therapeutischer Artikel nach Anspruch 13, wobei der Film ein Hydrogel ist.
- 50 15. Therapeutischer Artikel nach Anspruch 13, wobei der Film ein druckempfindlicher Klebstoff ist.